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10/030,378	11/09/2001	Jeffrey T. Blue	20455P	8714
210	7590	02/22/2006	EXAMINER	
MERCK AND CO., INC			LE, EMILY M	
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RAHWAY, NJ 07065-0907			PAPER NUMBER	
			1648	
DATE MAILED: 02/22/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/030,378

Applicant(s)

BLUE, JEFFREY T.

Examiner

Emily Le

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 25 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8 and 18-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 and 18-25 is/are rejected.
- 7) ☒ Claim(s) 20, 21, 23 and 24 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Status of Claims***

1. Claims 20-25 are added. Claims 9-17 are cancelled. Claims 1-8 and 18-25 are pending and under examination.

### ***Claim Objections***

2. Claims 20-21 and 23-24 are objected to because of the following informalities: Claims 20-21 recite the term "preformed". Given the context that the cited term is used, it is presumed that the intended term is "performed", not "preformed". If this is correct, then appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
4. Claims 1-8 and 18-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential element(s), such omission amounting to a gap between the elements. See MPEP § 2172.01.

The claims recite a method of assaying for viral activity to determine viral stability and potency by the difference between caspase 3 activity in different samples.

However, the claims do not recite a nexus between the difference in caspase 3 activity and the determination of viral stability and potency. For instance, is viral stability and potency present, absent, significant, insignificant, substantial or insubstantial when caspase 3 activity is more or less in one formulation compared to another formulation? In the instant, the claims fail to provide a link between the two elements.

Additionally, at lines 3-5 of page 9 of the specification, Applicant stressed the importance of collecting data found within the linear range of the assay when investigating and comparing caspase 3 activity. Within the same paragraph as the cited passage, Applicant promotes the use of a 1-hour incubation period for caspase 3 activity to ensure the data collected to be meaningful. [Lines 9-10 of page 9] In the instant, the specification clearly promotes the importance of collecting caspase 3 activity within a particular incubation time period or duration. However, it is noted that this guidance is absent from the claims. The present claims are not limited to the application of the claimed method at any particular incubation period. Such requirement is omitted from the present claims.

Also, the following analysis is directed at the requirement set forth in the claims wherein caspase 3 activity of a virus in one formulation is compared to the caspase 3 activity of the same virus from another formulation. The claims do not set forth a standard or fixed evaluation condition (e.g., the use of the same cell type for the virus obtained from different formulations, and measurement of caspase 3 activity at the same or similar time interval after incubation) that must be conducted or maintained during the measurement of caspase 3 activity. In the instant, it is found that the installment of a standard or fixed evaluation condition is necessary to render a meaningful analysis. In the absence of a defined or set evaluation protocol, a meaningful comparison between caspase 3 activity cannot be ascertained.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 21 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims contain the following recitation: wherein said virus is removed from said formulation at two or more time intervals.

The above-cited recitation was introduced in Applicant's 11/25/05 submission.

However, after conducting a search of the specification for the above cited recitation and for derivatives thereof, the Office cannot find express, implicit nor inherent support for the cited recitation. Nor has Applicant specifically point out the support for the cited recitation. Thus, the claims are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicant is reminded that Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP § 2163.06. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Banki et al.<sup>1</sup>

In response to the rejection set for in the previous office action, Applicant amended the claims to indicate the use of caspase 3 activity as an indication of viral activity to measure virus stability and potency in either i) different formulations; or ii) a single formulation at two or more time intervals. Applicant also submits that Banki et al. measures caspase 3 activity to study HIV induced apoptosis.

Applicant's submission has been considered, however, it is not found persuasive. In the instant, the claims are directed to a process comprising the following active steps:

a) contacting cells that are susceptible to caspase 3 induction with a virus, wherein the virus induces caspase 3 activity, and

b) measuring said caspase 3 activity, wherein steps a) and b) are repeated at two or more time intervals. The claims also require that the caspase 3 activity be measured using a caspase 3 substrate linked to a fluorimetric or colorimetric moiety, wherein the substrate is Asp-Glu-Val-Asp (DEVD).

Banki et al. teaches a process comprising the following active steps:

a) contacting cells that are susceptible to caspase 3 induction with a virus, wherein the virus induces caspase 3 activity, and

b) measuring said caspase 3 activity, wherein steps a) and b) are repeated at two or more time intervals. [See particularly Figure 2 with caption, page 11946; 1<sup>st</sup> sentence, last full paragraph, page 11948; and Figure 5 with caption, page 11949]

Banki et al. measured caspase 3 activity using a caspase 3 substrate linked to a fluorimetric or colorimetric moiety, wherein the substrate is Asp-Glu-Val-Asp (DEVD).

In the instant, Banki et al. teaches the claimed invention. The claimed invention is directed at a method for measuring caspase 3 activity. And Banki et al. teaches a method of measuring caspase 3 activity. The method of Banki et al. is the same as those recited in the claims. Thus, Banki et al. teaches the claimed method. Therefore, Banki et al. anticipates the claimed invention.

Furthermore, the recitation “provides an indication of virus stability and potency” and derivation thereof do not state a condition that is material to patentability; thus, is not given weight. The cited recitation simply expresses the intended result of a process. Thus, Banki et al. does not need to express an intention or purpose that is the same as those recited in the claims to render the claims unpatentable. See MPEP § 2114.04, which states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure...The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a “whereby” clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.” *Id.* However, the court noted (quoting *Minton v. Nat 'l Ass 'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a “whereby clause in a

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<sup>1</sup> Banki et al. Molecular ordering in HIV-induced apoptosis. *The Journal of Biological Chemistry*. May 08,

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method claim is not given weight when it simply expresses the intended result of a process step positively recited.” Id.

Additionally, Applicant is reminded that the claims are not limited to a particular virus; thus, HIV is within the full breadth of the claims.

Therefore, for the reasons set for above, Applicant’s submission is not found persuasive. The claims remain anticipated by Banki et al.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 4-5 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banki et al., as applied to claims 1-3, in view of Duncan et al.<sup>2</sup>

In response to the above rejection, Applicant amended claims 4-5 to indicate the use of caspase 3 activity as an indication of viral activity to measure virus stability and potency in either i) different formulations; or ii) a single formulation at two or more time intervals. Applicant also submits that the skilled artisan would not be motivated to modify Duncan et al. to look at caspase 3 activity alone or in combination with other caspases, and that Duncan et al. teaches measuring of apoptosis by quantifying detached cells.

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1998; Vol. 273, No. 19, 11944-11953.

<sup>2</sup> Duncan et al. Rubella virus-induced apoptosis varies among cell lines and is modulated by Bcl-XI and caspase inhibitors. Virology, March 01, 1999, Vol. 255, 117-128.



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Applicant's submission has been considered, however, it is not found persuasive.

In the instant, the relevance of Banki et al. as it pertains to claims 1-3 is discussed above. To summarize, Banki et al. anticipates the method recited in claims 1-3. See above for a detailed discussion of Banki et al.

Claims 4-5 and 18-19 limit virus to measles, mumps or rubella virus; and the cells to Vero or RK-13 cells.

Duncan et al. teaches that Vero and RK13 cells are susceptible to caspase 3 activity. Duncan et al. also teaches that the rubella virus induces caspase 3 activity.

The difference between the claimed invention and the teaching of Duncan et al. is: Duncan et al. does not teach the measurement of caspase 3 activity.

However, the deficiency noted of Duncan et al. is compensated by Banki et al. Banki et al. teaches the measurement of caspase 3 activity to quantify virally induced apoptosis.

Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the teachings of Banki et al. with Duncan et al. One of ordinary skill in the art at the time the invention was made would have been motivated to so to quantify virally induced apoptosis. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the use of caspase 3 activity to quantify virally induced apoptosis is well known in the art.

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Furthermore, Applicant is reminded that claims 18-19 do not require the measurement of caspase 3 activity in i) different formulations; or ii) a single formulation at two or more time intervals.

11. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Banki et al., as applied to claims 1-3, in view of Wu et al.<sup>3</sup>

In response to the above rejection, Applicant amended the claim to indicate the use of caspase 3 activity as an indication of viral activity to measure virus stability and potency in either i) different formulations; or ii) a single formulation at two or more time intervals.

Applicant's submission has been considered, however, it is not found persuasive. In the instant, Banki et al. teaches the invention set forth in claims 1-3, which includes the measurement of caspase 3 activity of a single formulation at two or more time intervals. See above for a detailed discussion of Banki et al. It is noted that Banki et al. does not teach the method of claim 6, which requires the virus present in claims 1-3 to be lyophilized. However, the deficiency noted of Banki et al. is fully compensated by Wu et al., which is detailed in the previous office action.

12. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Banki et al., as applied to claims 1-3, in view of Goodrich, Jr. et al.<sup>4</sup>

In response to the above rejection, Applicant amended the claim to indicate the use of caspase 3 activity as an indication of viral activity to measure virus stability and

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<sup>3</sup> Wu et al. U.S. Patent No. 6,689,600, which claims priority to U.S. Provisional No. 60/108606 [lines 5-10, page 3].

<sup>4</sup> Goodrich, Jr. et al. U.S. Patent No. 5958670.

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potency in either i) different formulations; or ii) a single formulation at two or more time intervals.

Applicant's submission has been considered, however, it is not found persuasive. In the instant, Banki et al. teaches the invention set forth in claims 1-3, which includes the measurement of caspase 3 activity of a single formulation at two or more time intervals. See above for a detailed discussion of Banki et al.

It is noted that Banki et al. does not teach the method of claim 8, which requires the cells present in claims 1-3 to be frozen then thawed. However, the deficiency noted of Banki et al. is fully compensated by Goodrich, Jr. et al., which is detailed in the previous office action.

13. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Banki et al., as applied to claim 18, in view of Esolen et al.<sup>5</sup>

Claim 22, which depends on claim 18, limits the virus to measles or mumps virus.

The relevance of Banki et al. as it pertains to claim 18 is discussed above. Banki et al. teaches a method of measuring caspase 3 activity to quantify virally induced apoptosis. The virus Banki et al. teaches is not measles or mumps. However, the deficiency noted of Banki et al. is compensated by Esolen et al. Esolen et al. teaches that measles virus induces apoptosis.

Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the teachings of Banki et al. and Esolen et al. One of ordinary skill in the art at the time the invention was made would have been

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motivated to do so to quantify apoptosis induced by the measles virus. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the use of caspase 3 activity to quantify virally induced apoptosis is well known in the art.

14. Claims 1, 20, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banki et al., as applied to claim 18, in view of Wu et al.

The claims require the measurement of caspase 3 activity be conducted for one virus obtained from two different formulations.

The relevance of Banki et al. as it pertains to claim 18 is discussed above. As noted in the above paragraphs, Banki et al. teaches a method of measuring caspase 3 activity to quantify virally induced apoptosis. The difference between the claimed invention and Banki et al. is that Banki et al. does not measure caspase 3 activity induced by the virus obtained from two different formulations.

However, Wu et al. does teach the significance of formulations on the biological activity and structural integrity of viral particles. [Lines 26-30 of page 2]

Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to compare different viral formulations. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to determine the effects of the formulation on the biological activity and structural integrity of the virus. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because

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<sup>5</sup> Esolen et al. Apoptosis as a cause of death in measles virus-infected cells. Journal of Virology, 1995,

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Banki et al. teaches the measurement of caspase 3 activity to quantify virally induced apoptosis.

***Conclusion***

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



E. Le



Jeffrey S. Parkin, Ph.D.  
Primary Patent Examiner  
Art Unit 1648